Studies on Uracil Derivatives and Analogs. Syntheses of 5-(β-Trimethylsilyl)ethynyluracil and 5-Ethynyluracil

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5-(α-Chlorovinyl)-2,4-dichloropyrimidine (I) on treatment with sodium methoxide in methanol was converted to 2,4-dimethoxy-5-ethynylpyrimidine (II) which was silylated by *t*-butyl lithium and chlorotrimethylsilane to 2,4-dimethoxy-5-(β-trimethylsilyl)ethynylpyrimidine (IV). Compound IV on deblocking with trimethylsilyl iodide yielded 5-(β-trimethylsilyl)ethynyluracil (V), which on treatment with sodium hydroxide in methanol was converted to 5-ethynyluracil (VI).

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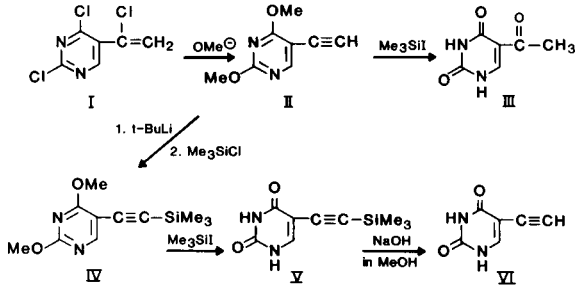
Introduction.

5-Substituted derivatives of uracil have been of great importance as anticancer agents (1) and also as antiviral agents (2-5). Similarly 5-substituted derivatives of orotic acid have pronounced inhibitory effect on the biosynthesis of pyrimidine (6,7). Recently (8,9) we have been interested in the synthesis of various 5-substituted derivatives of uracil and orotic acid and their 5,6-dihydro derivatives. In that connection, we needed large quantities of 5-ethynyluracil (VI). This paper reports an alternative procedure for the synthesis of 5-ethynyluracil (VI) and its 5-(β-trimethylsilyl) derivative (V), which is adaptable to large scale synthesis.

Results.

The synthesis of 5-ethynyluracil has been reported by two groups of workers (10,11). We have developed a procedure for the large scale synthesis of this compound. When 5-(α-chlorovinyl)-2,4-dichloropyrimidine (I) (11) was refluxed with sodium methoxide in absolute methanol, a quantitative conversion to 2,4-dimethoxy-5-ethynylpyrimidine (II) was accomplished. In contrast to the observation of Barr and co-workers (11) in the case of treatment of compound I with sodium ethoxide in ethanol, we did not see any significant formation of monomethoxy derivatives. Trimethylsilyl iodide has been successfully used for the deblocking of methyl ethers (12,13). However when we used trimethylsilyl iodide to deblock compound II, we found that it is converted in an excellent yield to 5-acetyluracil (III). We think that during the deblocking procedure, additon of hydriodic acid or trimethylsilyl iodide to the triple bond takes place and then the intermediates on hydrolysis lead to the formation of 5-acetyluracil (III).

The acetylene moiety could, however, be protected by silylation. 2,4-Dimethoxy-5-ethynyl pyrimidine (II) on treatment with *t*-butyllithium followed by chlorotrimethylsilane led to 2,4-dimethoxy-5-(β-trimethylsilyl)ethynylpyrimidine (IV) in good yield (80%). The formation of IV could be easily seen from the disappearance of signal due to ethynyl hydrogen (δ 3.32) and the appearance of signal due to the trimethylsilyl group (δ 0.25) in nmr. Compound IV on deblocking with trimethylsilyl iodide in chloroform led to 5-(β-trimethylsilyl) ethynyluracil (V) in 85% yield. Treatment of V with sodium hydroxide in methanol led to its conversion to 5-ethynyluracil (VI) in excellent yield.



Discussion.

We are reporting an alternative procedure for the synthesis of 5-ethynyl uracil (VI) starting from 5-(α-chlorovinyl)-2,4-dichloropyrimidine (I). Although there are more steps involved in our procedure, we have found overall yield is considerably better than that reported by Barr and co-workers (11), particularly in large scale preparations. We also report the synthesis of 5-(β-trimethysilyl)ethynyluracil (V). Although this compound has been mentioned before (14), its synthesis and physical characteristics have not been reported. In view of the reported importance of the nucleosides of 5-ethynyluracil as anticancer (15) agent we feel the nucleosides of compound V will be of considerable interest (16), and experiments are in progress in that direction.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ultraviolet spectra were recorded on a Beckman Model 25. Spectra were taken in 95% ethanol unless otherwise mentioned. The infrared spectra were done on a Beckman 4210 in a

fluorinated hydrocarbon. The ^1H nmr spectra (reported in δ) were recorded on a Varian EM-390 90-MHz nmr spectrometer in deuterated chloroform, using tetramethylsilane as internal reference. Elemental analyses were performed by Galbraith Laboritories, Inc., Knoxville, Tenn., or Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectra were taken on a Hewlett-Packard, Model 5985 spectrophotometer. Tlc was performed on an Eastman Chromagram sheet (6060 silica gel with fluorescent indicator) in the indicated solvents: solvent A, chloroform; solvent B, dichloromethane-ethylacetate (15:1); solvent C, chloroform-methanol (10:1).

2,4-Dimethoxy-5-ethynyl pyrimidine (II).

5-(α-Chlorovinyl)-2,4-dichloropyrimidine (11) (I) (50 g, 0.24 mole was added dropwise to a solution of sodium methoxide in absolute methanol (made by dissolving 24 g of sodium in 400 ml of dry methanol). The mixture was refluxed with stirring for 20 hours. Methanol was removed and the residue was treated with ice-water (200 ml) and extracted with dichloromethane (3 × 200 ml). The dichloromethane layer was washed with water, dried (magnesium sulfate) and solvent was removed to yield a crystalline residue, single spot on tlc, R_f = 0.71 in chloroform. This was crystallized from methanol into slightly pinkish plates (35 g, 0.21 mole, 87%), mp 83-84°; uv 275 (4,200) 243 (9,060); ir: 3270 cm^{-1} (≡C-H), 2120 cm^{-1} (C≡C); nmr (deuteriochloroform): δ 3.32 (s, 1H, -C≡C-H), 4.02 and 4.08 (2s, 6H, 2-OCH_3) and 8.36 (s, 1H, C_6-H); ms: 164 (M^+).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.65; H, 4.85; N, 1698.

Reaction of 2,4-Dimethoxy-5-ethynylpyrimidine (II) With Trimethylsilyl Iodide.

A mixture of compound II (5.0 g, 30 mmoles) and trimethylsilyl iodide (9.5 ml) in chloroform (80 ml) was refluxed for 2 hours under nitrogen atmosphere. The mixture was evaporated under aspirator and then dried under vaccum. The residue was boiled with water (10 ml) and methanol (20 ml), cooled and filtered to yield a solid which was crystallized from methanol-water to a cream colored solid (4.5 g 29 mmoles, 97%), mp 294° dec (lit (17) 283-285°). The compound is identical with an authentic sample of 5-acetyluracil from ir, nmr and uv spectroscopic comparison.

2,4-Dimethoxy-5-(β-trimethylsilyl)ethynylpyrimidine (IV).

2,4-Dimethoxy-5-ethynylpyrimidine (II) (25 g, 0.15 mole) was dissolved in dry tetrahydrofuran (500 ml) and cooled in a dry ice-acetone bath. To the cooled solution, *t*-butyl lithium (75 ml, 2.1 *M* solution in pentane from Aldrich Chem. Co.) was added dropwise from a syringe under argon atmosphere when a pink solution was formed. The mixture was stirred for 15 minutes followed by addition of freshly distilled chlorotrimethylsilane (25 ml) when the color changed to yellow. The mixture was stirred in the cold bath for 2 hours and then was decomposed with glacial acetic acid (10 ml) when it turned deep pinkish. The solvent was removed under aspirator and the residue was partitioned between water and dichloromethane. The dichloromethane layer was dried and solvent was removed to yield a gum (40 g) which was purified by chromatography on silica gel (40-140 mesh). The silylated material is mostly eluted with petroleum ether (bp 40-60°) and later by dichloromethane. Some starting material (1.2 g) was also recovered. The silylated material has R_f = 0.78 whereas the starting material has R_f = 0.71 in solvent A. 2,4-dimethoxy-5-(β-trimethylsilyl)ethynylpyrimidine was crystallized from petroleum ether (bp 40-60°) in the cold in fine needles (28 g, 0.12 mole, 80%), mp 73-74°; uv: 280 (7,410), 253 (9,370); ir: 2170 cm^{-1} (C≡C); nmr (deuteriochloroform): δ 0.25 (s, 9H, -$Si(CH_3)_3$), 4.00 and 4.03 (2s, 6H, 2-OCH_3) and 8.32 (s, 1H, C_6-H); ms: 236 (M^+), 221 (M^+ - CH_3).

Anal. Calcd. for $C_{11}H_{16}N_2O_2Si$: C, 55.93; H, 6.78; N, 11.86; Si, 11.86. Found: C, 55.96; H, 6.80; N, 11.90; Si, 11.84.

5-(β-trimethylsilyl)ethynyluracil (V).

A mixture of 2,4-dimethoxy-5-(β-trimethylsilyl)ethynylpyrimidine (IV) (30 g, 0.13 mole) and trimethylsilyl iodide (55 g, 0.28 mole) in chloroform (500 ml) was refluxed for 2 hours under nitrogen atmosphere. The residue, obtained after removal of solvent and drying, was digested with water (100 ml) and methanol (200 ml), cooled in the refrigerator and filtered to yield a white solid, single spot on tlc, R_f = 0.77 in solvent C. This was crystallized from methanol into white fine glistening needles (22.5 g 0.11 mole, 85%), mp 275-276°; uv: 293 (11,000), 234 (12,000); ir: 3180 cm^{-1} (NH), 2160 cm^{-1} (C≡C); nmr (DMSO-d_6 deuterium oxide): δ 0.2 (s, 9H, Si $(CH_3)_3$), 7.55 (s, 1H, C_6-H); ms: 208 (M^+), 193 (M^+ - CH_3, 100%).

Anal. Calcd. for $C_9H_{12}N_2O_2Si$: C, 51.92; H, 5.77; N, 13.46; Si, 13.46. Found: C, 51.85; H, 5.89; N, 13.49; Si, 13.55.

5-Ethynyluracil (VI).

5-(β-Trimethylsilyl)ethynyluracil (8.5 g, 40 mmoles) was dissolved in methanol (800 ml). Sodium hydroxide (5 g, 125 mmoles) dissolved in water (40 ml) was added to the solution and the mixture was stirred for 3 hours when white solids separated. Methanol was removed and the residue was treated with water (75 ml) and the *p*H of the mixture was adjusted to 5. The solids were filtered and dried to yield a white solid, which was crystallized from methanol-water mixture to a cream colorerd solid (4.6 g, 34 mmoles, 85%), mp 320° dec, identical with an authentic 5-ethynyluracil sample from ir, uv, nmr and ms comparison.

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